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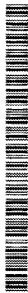
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(54) Title: OPHTHALMIC AND OTORHINOLARYNGOLOGICAL DEVICE MATERIALS

(57) Abstract: Disclosed are improved soft, high refractive index, acrylic device materials having an elongation of at least 150%. These materials, especially useful as intraocular lens materials, contain two principal monomers: an aryl acrylic hydrophobic monomer and a hydrophilic monomer.

OPHTHALMIC AND OTORHINOLARYNGOLOGICAL DEVICE MATERIALS

Field of the Invention

This invention is directed to improved ophthalmic and otorhinolaryngological device materials. In particular, this invention relates to soft, high refractive index acrylic device materials particularly suited for use as intraocular lens ("IOL") materials.

Background of the Invention

With the recent advances in small-incision cataract surgery, increased emphasis has been placed on developing soft, foldable materials suitable for use in artificial lenses. In general, these materials fall into one of three categories: hydrogels, silicones, and acrylics.

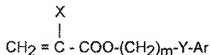
In general, hydrogel materials have a relatively low refractive index, making them less desirable than other materials because of the thicker lens optic necessary to achieve a given refractive power. Silicone materials generally have a higher refractive index than hydrogels, but tend to unfold explosively after being placed in the eye in a folded position. Explosive unfolding can potentially damage the corneal endothelium and/or rupture the natural lens capsule. Acrylic materials are desirable because they typically have a high refractive index and unfold more slowly or controllably than silicone materials.

U.S. Patent No. 5,290,892 discloses high refractive index, acrylic materials suitable for use as an IOL material. These acrylic materials contain, as principal components, two aryl acrylic monomers. The IOLs made of these acrylic materials can be rolled or folded for insertion through small incisions.

U.S. Patent No. 5,331,073 also discloses soft acrylic IOL materials. These materials contain as principal components, two acrylic monomers which are defined by the properties of their respective homopolymers. The

first monomer is defined as one in which its homopolymer has a refractive index of at least about 1.50. The second monomer is defined as one in which its homopolymer has a glass transition temperature less than about 22 °C. These IOL materials also contain a cross-linking component. Additionally, these materials may optionally contain a fourth constituent, different from the first three constituents, which is derived from a hydrophilic monomer. These materials preferably have a total of less than about 15% by weight of a hydrophilic component.

U.S. Patent No. 5,693,095 discloses foldable, high refractive index ophthalmic lens materials containing at least about 90 wt.% of only two principal components: one aryl acrylic hydrophobic monomer and one hydrophilic monomer. The aryl acrylic hydrophobic monomer has the formula



wherein: X is H or CH₃ ;

m is 0-6;

Y is nothing, O, S, or NR, wherein R is H, CH₃, C_nH_{2n+1} (n=1-10), iso-OC₃H₇, C₆H₅, or CH₂C₆H₅; and

Ar is any aromatic ring which can be unsubstituted or substituted with CH₃, C₂H₅, n-C₃H₇, iso-C₃H₇, OCH₃, C₆H₁₁, Cl, Br, C₆H₅, or CH₂C₆H₅.

The lens materials described in the '95 Patent preferably have a glass-transition temperature ("T_g") between about -20 and +25 °C.

Summary of the Invention

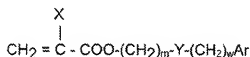
Improved soft, foldable acrylic device materials which are particularly suited for use as IOLs, but which are also useful as other ophthalmic or otorhinolaryngological devices, such as contact lenses, keratoprotheses, corneal rings or inlays, otological ventilation tubes and nasal implants, have been discovered. These materials contain only two principal components:

one aryl acrylic hydrophobic monomer and one hydrophilic monomer. The materials of the present invention are copolymers comprising at least about 90% by weight of the two principal monomeric components, provided that the amount of the hydrophilic component is not greater than that of the aryl acrylic hydrophobic component. The remainder of the material comprises up to 10% by weight of one or more additional components serving other purposes, such as cross-linking, UV-light absorbing, and blue-light absorbing components.

Detailed Description of the Invention

The improved acrylic materials of the present invention are copolymers comprising only two principal monomeric components: an aryl acrylic hydrophobic component and a hydrophilic component.

The aryl acrylic hydrophobic monomers suitable for use in the materials of the present invention have the formula



wherein: X is H or CH₃;

m is 2 – 6;

Y is O or O(CH₂CH₂O)_n;

n is 1 – 6;

w is 1 – 6, provided that m + w ≤ 8; and

Ar is any aromatic ring which can be unsubstituted or substituted with CH₃, C₂H₅, n-C₃H₇, iso-C₃H₇, OCH₃, C₆H₁₁, Cl, Br,

C₆H₅, or

CH₂C₆H₅.

Monomers of the above structural formula can be made by methods known in the art. For example, the conjugate alcohol of the desired monomer can be combined in a reaction vessel with methyl methacrylate, tetrabutyl titanate (catalyst), and a polymerization inhibitor such as 4-benzyloxy phenol.

The vessel can then be heated to facilitate the reaction and distill off the reaction by-products to drive the reaction to completion. Alternative synthesis schemes involve adding methacrylic acid to the conjugate alcohol and catalyzing with a carbodiimide or mixing the conjugate alcohol with
5 methacryloyl chloride and a base such as pyridine or triethylamine.

Preferred aryl acrylic hydrophobic monomers for use in the materials of the present invention are those wherein X is CH_3 , m is 2 - 5, w is 1, Y is O or $\text{OCH}_2\text{CH}_2\text{O}$, and Ar is phenyl. Most preferred are 2-benzyloxyethyl
10 methacrylate, 3-benzyloxypropyl methacrylate, and benzyloxyethoxyethyl methacrylate.

The homopolymers of the aryl acrylic hydrophobic monomers suitable for use in the present invention contain an equilibrium water content of less
15 than 3 %, and preferably less than 2 %, by weight as determined gravimetrically in deionized water at ambient conditions.

The hydrophilic monomers suitable for use in the present invention contain at least one reactive, unsaturated functional group. Preferably, the
20 reactive unsaturated functional group is a vinyl, acrylate or methacrylate group.

The homopolymers of the hydrophilic monomers suitable for use in the materials of the present invention have an equilibrium water content of at
25 least 10 %, and preferably at least 25 %, by weight as determined gravimetrically in deionized water at ambient conditions.

Suitable hydrophilic monomers for use in the present invention include 2-hydroxyethyl acrylate; 2-hydroxyethyl methacrylate; 2-N-ethylacrylate
30 pyrrolidone; 2-hydroxy-3-phenoxypropyl acrylate; 2,3-dihydroxypropyl acrylate; 2,3-dihydroxypropyl methacrylate; 2-N-vinyl pyrrolidone; polyethylene oxide:200 monomethyl ether monomethacrylate; polyethylene

oxide:200 monomethacrylate; polyethylene oxide:1000 monomethacrylate; hydroxyphenoxypropyl methacrylate and methoxyethoxyethyl methacrylate.

Preferred hydrophilic monomers for use in the present invention are
5 include 2-hydroxyethyl acrylate; 2-hydroxyethyl methacrylate; and polyethylene oxide:1000 monomethacrylate.

The materials of the present invention are copolymers comprising a total of about 90 % by weight of the two principal components described
10 above, provided that the amount of the hydrophilic component is not greater than the aryl acrylic hydrophobic component.

The copolymer materials of the present invention are cross-linked. The copolymerizable cross-linking agent used in the copolymers of this invention
15 may be any terminally ethylenically unsaturated compound having more than one unsaturated group. Combinations of cross-linking monomers are also suitable. Suitable cross-linking agents include, for example: ethylene glycol dimethacrylate; diethylene glycol dimethacrylate; polyethylene oxide dimethacrylate; allyl methacrylate; 1,3-propanediol dimethacrylate; allyl
20 methacrylate; 1,6-hexanediol dimethacrylate; 1,4-butanediol dimethacrylate; and their corresponding acrylates. Preferred cross-linking agents are 1,4-butanediol diacrylate (BDDA), ethyleneglycol dimethacrylate and polyethylene oxide dimethacrylate. Generally, the amount of the cross-linking component is at least 0.1 % (weight).

25 In addition to an aryl acrylic hydrophobic monomer, a hydrophilic monomer, and one or more cross-linking components, the lens material of the present invention may also contain a total of up to about 10 % by weight of additional components which serve other purposes, such as reactive UV and/or
30 blue-light absorbers.

A preferred reactive UV absorber is 2-(2'-hydroxy-3'-methallyl-5'-methylphenyl)benzotriazole, commercially available as o-Methallyl Tinuvin P

("oMTP") from Polysciences, Inc., Warrington, Pennsylvania. UV absorbers are typically present in an amount from about 0.1 - 5 % (weight).

Suitable reactive blue-light absorbing compounds are those described in commonly assigned, copending U.S. patent application serial number 08/138,663, the entire contents of which are hereby incorporated by reference. Blue-light absorbers are typically present in an amount from about 0.01 - 0.5 % (weight).

Suitable polymerization initiators include thermal initiators and photoinitiators. Preferred thermal initiators include peroxy free-radical initiators, such as t-butyl (peroxy-2-ethyl)hexanoate and di-(tert-butylcyclohexyl) peroxydicarbonate (commercially available as Perkadox[®] 16 from Akzo Chemicals Inc., Chicago, Illinois). Particularly in cases where the materials of the present invention do not contain a blue-light absorbing chromophore, preferred photoinitiators include benzoylphosphine oxide initiators, such as 2,4,6-trimethyl-benzoyldiphenyl-phosphine oxide, commercially available as Lucirin[®] TPO from BASF Corporation (Charlotte, North Carolina). Initiators are typically present in an amount of about 5 % (weight) or less.

The particular combination of the two principal monomers described above and the identity and amount of any additional components are determined by the desired properties of the finished ophthalmic lens. Preferably, the ingredients and their proportion are selected so that the improved acrylic lens materials of the present invention possess the following properties, which make the materials of the present invention particularly suitable for use in IOLs which are to be inserted through incisions of 5 mm or less.

The lens material preferably has a refractive index in the dry state of at least about 1.50 as measured by an Abbe' refractometer at 589 nm (Na light source). Optics made from materials having a refractive index lower than 1.50 are necessarily thicker than optics of the same power which are made from

materials having a higher refractive index. As such, IOL optics made from materials having a refractive index lower than about 1.50 generally require relatively larger incisions for IOL implantation.

5 The glass-transition temperature ("Tg") of the lens material, which affects the material's folding and unfolding characteristics, is preferably less than about +25 °C, and more preferably less than about +15 °C. Tg is measured by differential scanning calorimetry at 10 °C/min., and is generally determined at the midpoint of the transition of the heat flux curve. "Tg" and "Tg (mid)" both
10 refer to the Tg taken at the midpoint of the transition of the heat flux curve. "Tg (start)" refers to the Tg taken at the beginning of the transition of the heat flux curve; "Tg (end)" refers to the Tg taken at the end of the transition of the heat flux curve.

15 The lens material will have an elongation of at least 150%, preferably at least 200%, and most preferably between 300 and 600%. This property indicates that the lens generally will not crack, tear or split when folded. Elongation of polymer samples is determined on dumbbell shaped tension test specimens with a 20 mm total length, length in the grip area of 4.88 mm,
20 overall width of 2.49 mm, 0.833 mm width of the narrow section, a fillet radius of 8.83 mm, and a thickness of 0.9 mm. Testing is performed on samples at standard laboratory conditions of 23 ± 2 °C and 50 ± 5 % relative humidity using an Instron Material Tester model 1122 with a 2000 gram load cell. The grip distance is set at 14 mm and a crosshead speed is set at 20 mm/minute
25 and the sample is pulled to 700 % elongation or until failure. The elongation (strain) is reported as a fraction of the displacement at failure to the original grip distance. The modulus is calculated as the instantaneous slope of the stress-strain curve at 100 % strain. Stress is calculated at the maximum load for the sample, typically the load when the sample breaks, assuming that the
30 initial area remains constant. This stress is recorded as "tensile strength" in the examples below.

IOLs constructed of the materials of the present invention can be of any design capable of being rolled or folded into a small cross section that can fit through a relatively smaller incision. For example, the IOLs can be of what is known as a one piece or multipiece design, and comprise optic and haptic components. The optic is that portion which serves as the lens and the haptics are attached to the optic and are like arms which hold the optic in its proper place in the eye. The optic and haptic(s) can be of the same or different material. A multipiece lens is so called because the optic and the haptic(s) are made separately and then the haptics are attached to the optic. In a single piece lens, the optic and the haptics are formed out of one piece of material. Depending on the material, the haptics are then cut, or lathed, out of the material to produce the IOL.

Most preferred for foldable IOLs are materials that have a tensile modulus (stress at break) < 10 Mpa and a Tg (end) < 30 °C.

In addition to IOLs, the materials of the present invention are also suitable for use as other ophthalmic or otorhinolaryngological devices such as contact lenses, keratoprotheses, corneal inlays or rings, otological ventilation tubes and nasal implants.

The invention will be further illustrated by the following examples which are intended to be illustrative, but not limiting.

Each of the formulations of Examples 1 – 14 is prepared as follows, with all of the reactive monomers used being substantially free of inhibitors. After combining the formulation components as listed in Table 1, each formulation is mixed by agitation, and then injected into a polypropylene 25 x 12 x 1 mm slab mold. The bottom portion of the IOL mold contains a cavity which is filled to capacity, and then the top portion of the IOL mold is placed on the bottom portion and locked in place by mating male and female grooves machined into each portion. To make slabs, the cavity in the bottom portion of the slab mold is filled to capacity with the formulation and then the top is

placed on strictly as a seal. The molds can either be filled under an inert nitrogen or standard laboratory atmosphere. To maintain the mold geometry during curing, a means of clamping via springs is asserted on the molds. The clamped molds are placed in a convection air oven and cured at 80 – 90 °C for 1 hour, then 100 – 110 °C for 2 hours. At the end of polymerization period, the molds are opened and the cured intraocular lenses or polymer slabs are removed and extracted in acetone to remove any unreacted materials.

The physical properties of the cured materials shown in Tables 1 and 2 are then assessed (according to the protocols referred to above). Unless otherwise indicated, all ingredient amounts are listed as % by weight.

TABLE 1

Ingredient	Example No.					
	1	2	3	4	5	6
PPMA	84.50	84.51	84.44	---	---	---
BPMA	---	---	---	84.54	84.50	84.41
HEMA	14.99	---	---	14.96	---	---
MEMA	---	14.97	---	---	15.01	---
HPMA	---	---	15.06	---	---	15.01
EGDMA	0.51	0.52	0.50	0.51	0.49	0.57
BPO	0.95	0.97	0.91	0.94	0.95	0.93
Tensile Strength (MPa)	9.1	3.97	6.93	8.64	2.93	6.02
% Strain	325	834	586	392	822	529
Young's Modulus (MPa)	22.6	1.4	10.5	14.8	1.04	7.72
100% Modulus (MPa)	9.41	0.79	5.04	7.9	0.59	4.14

PPMA: 5-phenylpentyl methacrylate

BPMA: 2-benzoyloxyethyl methacrylate

HEMA: hydroxyethyl methacrylate

MEMA: methoxyethoxyethyl methacrylate

HPMA: hydroxyphenoxypropyl methacrylate

EGDMA: ethylene glycol dimethacrylate

BPO: benzoyl peroxide

TABLE 2

Ingredient	Example No.							
	7	8	9	10	11	12	13	14
PPMA	84.30	84.48	---	---	---	---	---	---
BPMA	---	---	83.87	---	---	---	---	---
PBMA	---	---	---	84.45	84.48	---	---	---
BEMA	---	---	---	---	---	84.44	84.49	---
BEEMA	---	---	---	---	---	---	---	84.5
MEMA	15.13	---	14.88	15.01	---	14.99	---	---
HEMA	---	14.98	---	---	15.00	---	15.02	15.1
EGDMA	0.57	0.54	1.25	0.54	0.52	0.57	0.49	0.4
t-BPO	1.07	1.05	1.18	1.01	1.01	1.03	1.03	1.3
Tensile Strength (MPa)	5.1	10.3	4.8	7.1	23.6	7.1	24.3	4.6
% Strain	823.4	371.2	537.2	846.4	40.6	648.8	41.0	681
Young's Modulus (MPa)	1.6	24.7	2.0	6.3	31.0	7.8	75.9	1.4
T _g (start) °C	-25	-33	-27	-30	-27	-25	-18	---
T _g (end) °C	10	32	22	27	40	13	30	---
T _g (mid) °C	-10	3	-8	-4	16	2	15	-12.7

5

BEEMA: benzyloxyethoxyethyl methacrylate

PBMA: 4-phenylbutylmethacrylate

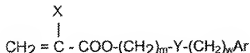
BEMA: 2-benzyloxyethyl methacrylate

t-BPO: t-butyl (peroxy-2-ethyl)hexanoate

10

We claim:

1. A copolymer having an elongation of at least 150%, comprising a total of at least 90 % by weight of two principal monomers, wherein one principal monomer is an aryl acrylic hydrophobic monomer of the formula



wherein: X is H or CH₃;

m is 2 - 6;

Y is O or O(CH₂CH₂O)_n;

n is 1 - 6;

w is 1 - 6, provided that m + w ≤ 8; and

Ar is any aromatic ring which can be unsubstituted or substituted with CH₃, C₂H₅, n-C₃H₇, iso-C₃H₇, OCH₃, C₆H₁₁, Cl, Br,

C₆H₅, or

CH₂C₆H₅;

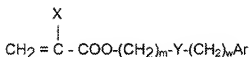
the homopolymer of which has an equilibrium water content of 3 % or less,

and the other principal monomer, present in an amount not greater than the amount of the aryl acrylic hydrophobic monomer, is a hydrophilic monomer having at least one reactive unsaturated functional group, the homopolymer of which has an equilibrium water content of at least 10 %,

and wherein the copolymer further comprises a cross-linking monomer having a plurality of polymerizable ethylenically unsaturated groups.

2. The copolymer of claim 1 wherein X is CH₃, m is 2 - 5, w is 1, Ar is phenyl, and Y is selected from the group consisting of O and OCH₂CH₂O.
3. The copolymer of Claim 2 wherein the aryl acrylic hydrophobic monomer is selected from the group consisting of 2-benzyloxyethyl methacrylate; 3-benzyloxypropyl methacrylate; and benzyloxyethoxyethyl methacrylate.
4. The copolymer of Claim 1 wherein the unsaturated functional group in the hydrophilic monomer is selected from the group consisting of vinyl; acrylate; and methacrylate groups.
5. The copolymer of Claim 4 wherein the hydrophilic monomer is selected from the group consisting of 2-hydroxyethyl acrylate; 2-hydroxyethyl methacrylate; 2-N-ethylacrylate pyrrolidone; 2-hydroxy-3-phenoxypropyl acrylate; 2,3-dihydroxypropyl methacrylate; 2-N-vinyl pyrrolidone; polyethylene oxide:200 monomethyl ether monomethacrylate; polyethylene oxide:200 monomethacrylate; polyethylene oxide:1000 monomethacrylate; hydroxyphenoxypropyl methacrylate and methoxyethoxyethyl methacrylate.
6. The copolymer of Claim 5 wherein the hydrophilic monomer is selected from the group consisting of 2-hydroxyethyl acrylate, 2-hydroxyethyl methacrylate, and polyethylene oxide:1000 monomethacrylate.
7. The copolymer of Claim 1 further comprising one or more components selected from the group consisting of reactive UV absorbers and reactive blue-light absorbers.
8. The copolymer of Claim 1 wherein the copolymer has a refractive index of at least 1.50.

9. The copolymer of Claim 1 wherein the copolymer has a Tg less than about +15 °C.
10. The copolymer of Claim 1 wherein the copolymer has an elongation of at least 150%, a tensile modulus < 10 Mpa, and a Tg (end) < 30 °C.
11. The copolymer of Claim 10 wherein the copolymer has an elongation from 300 to 600%.
12. An ophthalmic lens comprising a copolymer having an elongation of at least 150%, comprising a total of at least 90 % by weight of two principal monomers, wherein one principal monomer is an aryl acrylic hydrophobic monomer of the formula



wherein: X is H or CH₃;

m is 2 - 6;

Y is O or O(CH₂CH₂O)_n;

n is 1 - 6;

w is 1 - 6, provided that m + w ≤ 8; and

Ar is any aromatic ring which can be unsubstituted or substituted

with CH₃, C₂H₅, n-C₃H₇, iso-C₃H₇, OCH₃, C₆H₁₁, Cl, Br,

C₆H₅, or

CH₂C₆H₅;

the homopolymer of which has an equilibrium water content of 3 % or less,

and the other principal monomer, present in an amount not greater than the amount of the aryl acrylic hydrophobic monomer, is a hydrophilic monomer having at least one reactive unsaturated

functional group, the homopolymer of which has an equilibrium water content of at least 10 %.

and wherein the copolymer further comprises a cross-linking monomer having a plurality of polymerizable ethylenically unsaturated groups.

13. The ophthalmic lens of Claim 12 wherein the lens is an intraocular lens.

14. The intraocular lens of Claim 13 wherein X is CH₃, m is 2 - 5, w is 1, Ar is phenyl, and Y is selected from the group consisting of O and OCH₂CH₂O.

15. The intraocular lens of Claim 14 wherein the aryl acrylic hydrophobic monomer is selected from the group consisting of 2-benzyloxyethyl methacrylate; 3-benzyloxypropyl methacrylate; and benzyloxyethoxyethyl methacrylate.

16. The intraocular lens of Claim 14 wherein the unsaturated functional group in the hydrophilic monomer is selected from the group consisting of vinyl, acrylate, and methacrylate groups.

17. The intraocular lens of Claim 16 wherein the hydrophilic monomer is selected from the group consisting of 2-hydroxyethyl acrylate; 2-hydroxyethyl methacrylate; 2-N-ethylacrylate pyrrolidone; 2-hydroxy-3-phenoxypropyl acrylate; 2,3-dihydroxypropyl methacrylate; 2-N-vinyl pyrrolidone; polyethylene oxide:200 monomethyl ether monomethacrylate; polyethylene oxide:200 monomethacrylate; and polyethylene oxide:1000 monomethacrylate; hydroxyphenoxypyl methacrylate and methoxyethoxyethyl methacrylate.

18. The intraocular lens of Claim 17 wherein the hydrophilic monomer is selected from the group consisting of 2-hydroxyethyl acrylate, 2-

hydroxyethyl methacrylate, and polyethylene oxide:1000 monomethacrylate.

- 5 19. The intraocular lens of Claim 12 further comprising one or more components selected from the group consisting of reactive UV absorbers and reactive blue-light absorbers.
20. The intraocular lens of Claim 12 wherein the copolymer has an elongation of at least 150%, a tensile modulus < 10 Mpa, and a Tg
10 (end) < 30 °C.

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/US 00/23285

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C08F220/30 C08F220/18 G02B1/04 A61L27/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C08F G02B A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 40303 A (ALCON LAB INC) 19 December 1996 (1996-12-19) claims 1-29 page 4, line 4 - page 5, line 17 ---	1,2, 4-13,19, 20
X	US 5 693 095 A (JINKERSON DAVID L ET AL) 2 December 1997 (1997-12-02) cited in the application claims 1-29 column 1, line 52 - column 2, line 3 column 2, line 32 - line 38 column 2, line 44 - column 3, line 38 ---	1,2, 4-13,19, 20
A	US 5 331 073 A (WEINSCHENK III JOSEPH I ET AL) 19 July 1994 (1994-07-19) cited in the application claims 1,8 ---	1
-/-		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not

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Date of the actual completion of the international search

31 October 2000

Date of mailing of the international search report

21/12/2000

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INTERNATIONAL SEARCH REPORT

International Application No.

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Category	Citation of document, with indication where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

Information on patent family members

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